REMARKS/ARGUMENTS

Claims 1-4, 6-12, 14-17 and 37 are under examination in the application. The Office Action mailed on June 14, 2007, includes the following objections and rejections:

1. Claim 37 is rejected under 35 U.S.C. § 112 first paragraph;
2. Claims 1-4, 6, 8, 9, 15-17 and 37 are rejected under 35 U.S.C. § 102 as being as anticipated.
3. Claims 1-4, 6, 7, 9, and 14-16 are rejected under 35 U.S.C. § 102 as being anticipated.
4. Claims 1, 7, and 10-12 are rejected under 35 U.S.C. § 102 as being anticipated.

Applicants assert that the rejection under 35 U.S.C. § 103 as listed in the Office Action mailed November 3, 2006 has not been advanced in the Office Action of June 14, 2007, and as such is considered withdrawn.

Claim 37 is rejected under 35 U.S.C. § 112, Second Paragraph

The Action rejects claim 37 under 35 U.S.C. § 112 Second Paragraph as being indefinite. Claim 37 as amended fully complies with 35 U.S.C. § 112. Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §112.

The Applicants disagree with the interpretation of claim 37 and (and claims 1-4, 6-12, 14-17 on the same grounds) in the Action. Claim 37 of the present application provides an isolated thioaptamer that mediates gene silencing. The isolated thioaptamer includes a partially thiomodified phosphodiester backbone having one or more of the following rAMP(αS), rUMP(αS), rGMP(αS), rCMP(αS), rAMP(αS2), rUMP(αS2), rGMP(αS2) or rCMP(αS2). The phosphodiester backbone has been modified by the addition of one or more of the following rATP(αS), rUTP(αS), rGTP(αS), rCTP(αS), rATP(αS2), rUTP(αS2), rGTP(αS2) or rCTP(αS2) to form a partially thiomodified phosphodiester backbone. Once the modified nucleotide has been added to the phosphodiester backbone it is in the form of a rAMP(αS), rUMP(αS), rGMP(αS), rCMP(αS), rAMP(αS2), rUMP(αS2), rGMP(αS2) or rCMP(αS2). The claims have been amended to more specifically point out and distinctly claim the subject matter the inventor regards as the invention.

This amendment finds support throughout the application, specifically, the application (paragraphs

[0030-0031]) defines the term thioaptamer as oligonucleotides (ODNs) in which one or more of the four constituent nucleotide bases of an oligonucleotide are analogues of nucleotides that normally form the DNA or RNA backbones. The analogues include thiophosphates having sulphur in place of one or more of the non bridging oxygens bound to the phosphorus. For example, monothiophosphates (αS) have only one sulfur and are thus chiral around the phosphorus center; while dithiophosphates (αS2) are substituted at both oxygens and are thus achiral. The modified nucleotide thioaptamer include one or more monophosphorothioate (e.g., dATP(αS), dTTP(αS), dCTP(αS), dGTP(αS), rUTP (αS), rATP(αS), rCTP(αS) or rGTP(αS)) or phosphordithioate (e.g., dATP(αS2), dTTP(αS2), dCTP(αS2), dGTP(αS2), rATP(αS2), rCTP(αS2), rGTP(αS2) or rUTP(αS2)) linkages incorporation by polymerases.

Applicants assert that claim 37 as amended fully complies with the written description requirement of 35 U.S.C. § 112 first paragraph. Applicant respectfully requests the withdrawal of the rejection under 35 U.S.C. § 112.

Claim 37 is rejected under 35 U.S.C. § 112, First Paragraph

The Action also rejects claim 37 under 35 U.S.C. § 112 as failing to comply with the enablement requirement. Applicants disagree with the interpretation of Opalinska, et al. and asserts that the present application fully complies with the enablement requirement under 35 U.S.C. § 112.

Specifically, the Action states that the present disclosure lacks a demonstrated therapeutic effect and lacks the evidence to show the composition may act therapeutically. Page 8 of the Action states:

> therapeutically effective. While some nucleic acids have proceeded to clinical trials or have been approved for drug use, the rejection is based in part on the lack of a demonstrated therapeutic effect for the particular claimed oligonucleotides and the ability of other nucleic acids to act therapeutically does not lead the skilled artisan to recognize the instantly claimed nucleotides to act as a therapeutic

The present application provides sufficient evidence of a therapeutic effect and discloses the use of the composition for treatments. The present application (paragraph [0080]) provides evidence that the

testing of aptamers for antiviral activity and includes testing in cell culture using HeLA cells. As the HeLa cell line was derived for use in cancer research and there is sufficient correlation between the cell studies and treatments. "Correlation" as used herein refers to the relationship between *in vitro* or *in vivo* animal model assays and a disclosed or a claimed method of use. An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications). The Action presents no evidence against correlation. Thus, based upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence. (Citations omitted.)

Furthermore, in addition to being instructed that this composition may be used as a pharmaceutical treatment, the skilled artisan knows that such compositions may be used as treatments as evidenced by other compositions in the art. This is evidenced by Opalinska, et al. in the Office action. Regardless of problems, Opalinska, et al. clearly states on page 511, states "...oligonucleotides can escape from the vesicles intact, enter the cytoplasm and then diffuse into the nucleus..." Opalinska, et al. also states that these techniques have been successfully used both *in-vivo* and *in-vitro* (see Opalinska, et al. second paragraph page 504). Opalinska, et al., even states that "...these small molecules have the ability to diffuse into the nucleus where they can contact dsDNA..." (see Opalinska, et al. page 504). Therefore it is clearly in the scope of the skilled artisan. It is not necessary to "enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect." CFMT, Inc. v. Yieldup Int'l Corp., 349 F.3d 1333, 1338, 68 USPQ2d 1940, 1944 (Fed. Cir. 2003) (an invention directed to a general system to improve the cleaning process for semiconductor wafers was enabled by a disclosure showing improvements in the overall system).

To further illustrate the use of such compositions and thus the skilled artisan's knowledge, Opalinska, et al. discusses numerous oligonucleotide treatments which are in clinical trials (see Opalinska, et al. Table 2 on page 511) and that both European and United States authorities have approved a nucleic-acid drug for use to treat a viral infection of the eye (Opalinska, et al. on page 507). The Action states that "the majority of clinical trials cited in the Opalinska reference are phase I and phase II." The mere

fact that there are clinical trials, regardless of the phase of clinical trials, clearly illustrates that of such compounds are being used for treatments and that the skilled artisan understands that such compositions may be used in such treatments and that such compositions may be used to deliver compositions to the desired location for treatment. It is not necessary for the specification to teach the exact concentration that must be administer to the each and every patient to provide the specific plasma concentration (or cellular or nuclear concentration) for the composition, as that is within the scope of the knowledge of the skilled artisan.

As such, the specification satisfies the written description requirement under 35 U.S.C. § 112, first paragraph. For the reasons mentioned above, the Applicants respectfully request the withdrawal of the rejection under 35 U.S.C. § 112.

Claims 1-4, 6, 8, 9, and 15-17 are rejected under 35 U.S.C. § 102

The Action rejects claims 1-4, 6, 8, 9, and 15-17 under 35 U.S.C. § 102(b) as being anticipated by Baracchini, et al. (US Patent number 5,801,154) ("Baracchini"). Applicants respectfully submit that the cited reference fails to meet the standard of 35 U.S.C. § 102(b) namely, teaching all elements of the claimed invention either explicitly or impliedly and every limitation of the present invention.

Baracchini does not identically disclose every element of the claimed invention. See Corning Glass Works v. Sumitomo Electric, 9 USPQ 2d 1962, 1965 (Fed. Cir. 1989). A reference that excludes a claimed element, no matter how insubstantial or obvious, is enough to negate anticipation. Connell v. Sears, Roebuck & Co., 220 USPQ 193, 198 (Fed. Cir. 1983).

The present invention provides an isolated thioaptamer that mediates gene silencing, wherein the isolated thioaptamer having a partially thiomodified phosphodiester backbone with one or more of the following rAMP(αS), rUMP(αS), rGMP(αS), rCMP(αS), rAMP(αS_2), rUMP(αS_2), rGMP(αS_2) or rCMP(αS_2) and is between 15 and 25 nucleotides. The present invention includes a partially thiomodified phosphodiester backbone, not a fully modified thiomodified phosphodiester backbone.

Baracchini teaches oligonucleotides that specifically hybridize with nucleic acids encoding multidrug resistance-associated protein (MRP) and are designed to bind either directly to mRNA or to a selected DNA portion forming a triple stranded structure, thereby modulating the amount of mRNA made from

the gene. In either case, expression of MRP protein is ultimately modulated. (column 3, lines 14-20). Baracchini teaches that the modifications may include phosphorotioates (column 6, line 36) but makes no indication that the modification may include a partially modified backbone. In addition, the examples provided in TABLE 1 includes "All are phosphorotioates" and therefore a partially thiomodified phosphodiester backbone is not discussed. And again Baracchini provides examples of oligonucleotides having a uniformed phosphodiester backbone having a central gap (column 12, lines 15-18). Baracchini does not disclose an isolated thioaptamer that mediates gene silencing, wherein the isolated thioaptamer having a partially thiomodified phosphodiester backbone with one or more of the following rAMP(αS), rUMP(αS), rGMP(αS), rCMP(αS), rAMP(αS_2), rUMP(αS_2), rGMP(αS_2) or rCMP(αS_2) and is between 15 and 25 nucleotides. Baracchini does not identically disclose every element of the claimed invention.

Applicants respectfully submit that claims 1-4, 6, 8, 9, and 15-17 as amended are not anticipated by Baracchini and even if they were Baracchini is non-enabling and does not disclose and enable each and every limitation to the present invention; and as such, cannot anticipate the present invention. Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 102(b).

Claims 1-4, 6, 7, 9, and 14-16 are rejected under 35 U.S.C. § 102

The Action rejects claims 1-4, 6, 7, 9, and 14-16 under 35 U.S.C. § 102(b) as being anticipated by Agrawal, et al. (WO 94/01550) ("Agrawal"). Applicants respectfully submit that the cited reference fails to meet the standard of 35 U.S.C. § 102(b) namely, teaching all elements of the claimed invention either explicitly or impliedly and every limitation of the present invention.

Agrawal does not identically disclose every element of the claimed invention. See Corning Glass Works v. Sumitomo Electric, 9 USPQ 2d 1962, 1965 (Fed. Cir. 1989). A reference that excludes a claimed element, no matter how insubstantial or obvious, is enough to negate anticipation. Connell v. Sears, Roebuck & Co., 220 USPQ 193, 198 (Fed. Cir. 1983).

The present invention provides an isolated thioaptamer that mediates gene silencing, wherein the isolated thioaptamer having a partially thiomodified phosphodiester backbone with one or more of the following rAMP(αS), rUMP(αS), rGMP(αS), rCMP(αS), rAMP(αS_2), rUMP(αS_2), rGMP(αS_2) or rCMP(αS_2) and is between 15 and 25 nucleotides.

In contrast, Agrawal teaches self-stabilized oligonucleotides that has two structural features a target hybridizing region and a self-complementary region that is complementary to a nucleic acid sequence within the oligonucleotide. In addition, the self-stabilized oligonucleotides form double stranded FULLY complimentary (self complimentary).

Agrawal clearly does not teach that the thioaptamer may have a partially thiomodified phosphodiester backbone with one or more of the following rAMP(αS), rUMP(αS), rGMP(αS), rCMP(αS), rAMP(αS_2), rUMP(αS_2), rGMP(αS_2) or rCMP(αS_2). The oligonucleotides of Agrawal are merely self complimentary and do not hybridize to a separate nucleic acid sequence. Applicants assert that the term phosphorothioate linkage is not interchangeable with the term monophosphate, clearly there are substiantial differences between the two that do not allow interchangeable or as equivalent use as stated in the Office Action.

Applicants respectfully submit that claims 1-4, 6, 7, 9, and 14-16 as amended are not anticipated by Agrawal. Agrawal is non-enabling and does not disclose and enable each and every limitation to the present invention; and as such, cannot anticipation the present invention. Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 102(b).

Claims 1, 7, and 10-12 are rejected under 35 U.S.C. § 102

The Action rejects claims 1-7 and 10-12 under 35 U.S.C. § 102(b) as being anticipated by Parrish, et al. (Molecular Cell 2000) ("Parrish"). Applicants respectfully submit that the cited reference fails to meet the standard of 35 U.S.C. § 102(b) namely, teaching all elements of the claimed invention either explicitly or impliedly and every limitation of the present invention.

Parrish fails to identically disclose every element of the claimed invention. See Corning Glass Works v. Sumitomo Electric, 9 USPQ 2d 1962, 1965 (Fed. Cir. 1989). A reference that excludes a claimed element, no matter how insubstantial or obvious, is enough to negate anticipation. Connell v. Sears, Roebuck & Co., 220 USPQ 193, 198 (Fed. Cir. 1983).

Parrish does not meet the standard of 35 U.S.C. § 102(b) namely, teaching all elements of the claimed invention. Parrish does not teach a partially thio-modified thioaptamer that mediates gene silencing with between 15 and 25 nucleotides; an isolated thioaptamer between 15 and 25 nucleotides having a partially thiomodified phosphodiester backbone having rAMP(αS), rUMP(αS), rGMP(αS), rCMP(αS),

rAMP(αS_2), rUMP(αS_2), rGMP(αS_2) or rCMP(αS_2). In fact, Parrish does not teach rAMP(αS_2), rUMP(αS_2), rGMP(αS_2) or rCMP(αS_2) for any sequence or any length.

Specifically, Parrish does not disclose a thioaptamer where all of the non-adjacent dA, dC, dG, or dT phosphate sites of the modified nucleotide aptamer are replaced with phosphorothioate groups; all of the non-adjacent dA, dC, dG, and dT phosphate sites of the modified nucleotide aptamer are replaced with phosphorothioate groups; or substantially all non-adjacent phosphate sites of the modified nucleotide aptamer are replaced with phosphorothioate groups. Parrish does not disclose, no more than three adjacent phosphate sites of the modified nucleotide aptamer are replaced with phosphorodithioate groups or that the thioaptamers may be obtained by adding bases enzymatically using a mix of four nucleotides, wherein one or more of the nucleotides are a mix of unmodified and thiophosphate-modified nucleotides, to form a partially thiophosphate-modified thioaptamer library. Parrish does not disclose thioaptamers made by adding bases to an oligonucleotide wherein a portion of the phosphate groups are thiophosphate-modified nucleotides, and where no more than three of the four different nucleotides are substituted on the 5'-phosphate positions by 5'-thiophosphates in each synthesized oligonucleotide are thiophosphate-modified nucleotides. (see paragraph [0031] of the present specification).

Applicants respectfully submit that claims 1-7 and 10-12 as amended are not anticipated by Parrish. Parrish is non-enabling and does not disclose and enable each and every limitation to the present invention; and as such, cannot anticipation the present invention. Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 102(b).

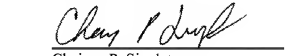
Conclusion

In light of the remarks and arguments presented above, Applicants respectfully submit that the claims in the Application are in condition for allowance. Favorable consideration and allowance of the pending claims is therefore respectfully requested.

If the Examiner has any questions or comments, or if further clarification is required, it is requested that the Examiner contact the undersigned at the telephone number listed below.

Dated: December 14, 2007

Respectfully submitted,



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